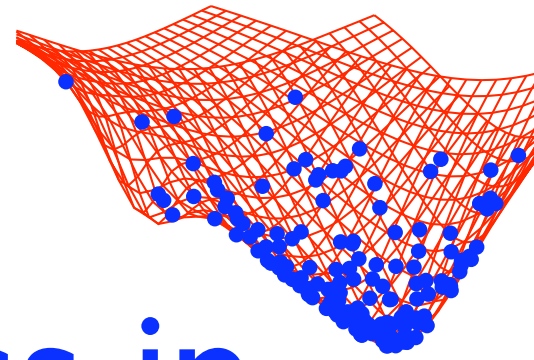


Cornell University
Laboratory of
Atomic and Solid State Physics



Universal Sloppiness in Complex Biology

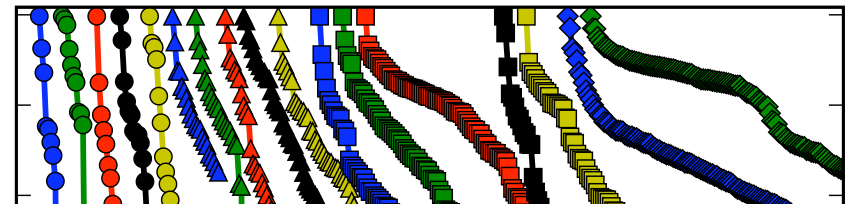
Implications for Modeling and Evolution

Ryan Gutenkunst

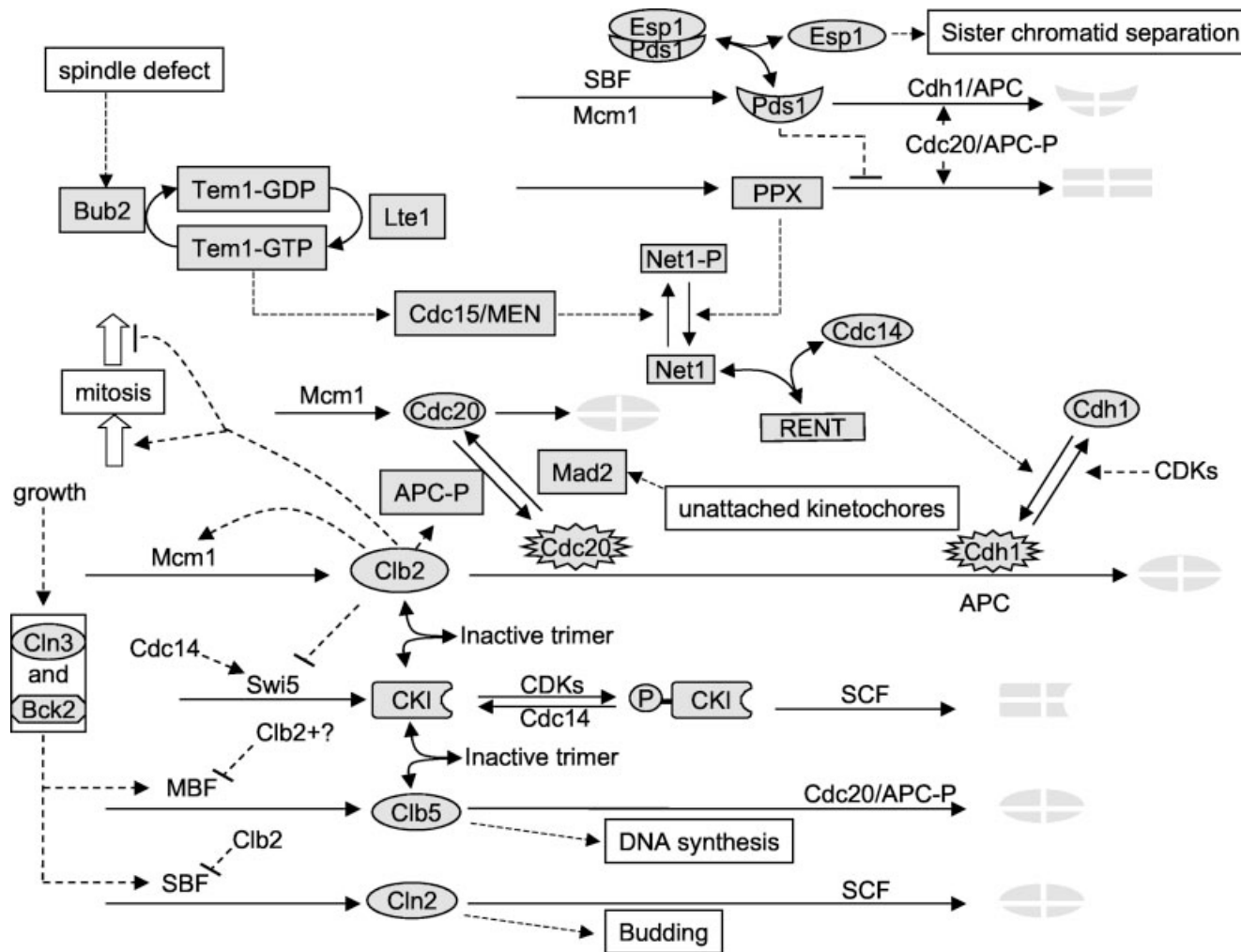
Josh Waterfall, Fergal Casey, Chris Myers, and Jim Sethna

Computational Biology Student Seminar

February 9th, 2007



Complex Biology



Chen et al. *Mol. Biol. Cell* 15:3841–3862 (2004)

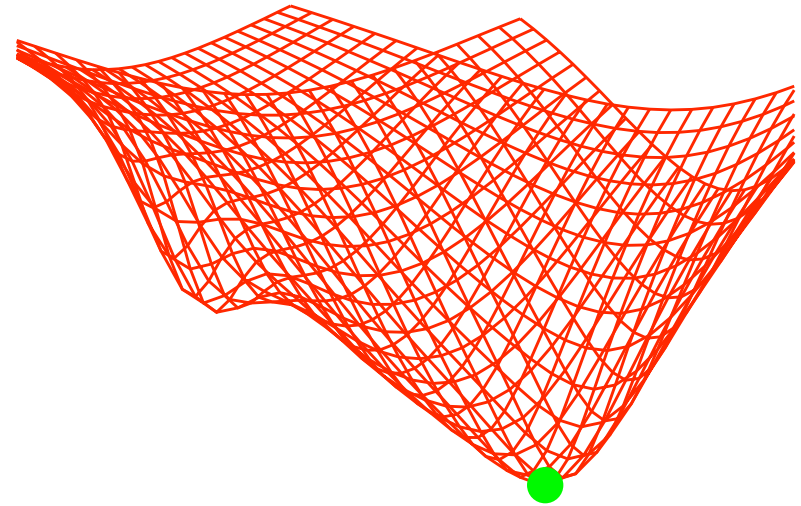
Budding yeast
cell cycle

Tyson group's
model has

131 free parameters

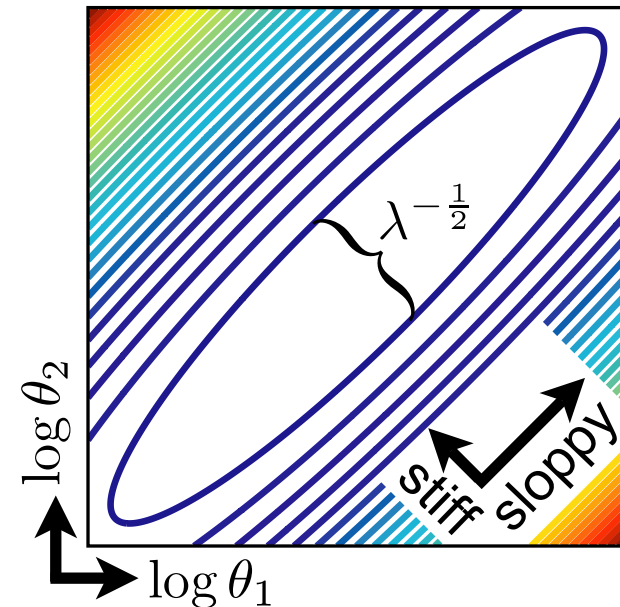
Parameter Sensitivities

$\chi^2(\theta)$: (scalar) measure of the difference in model behavior between parameters θ and θ^* .

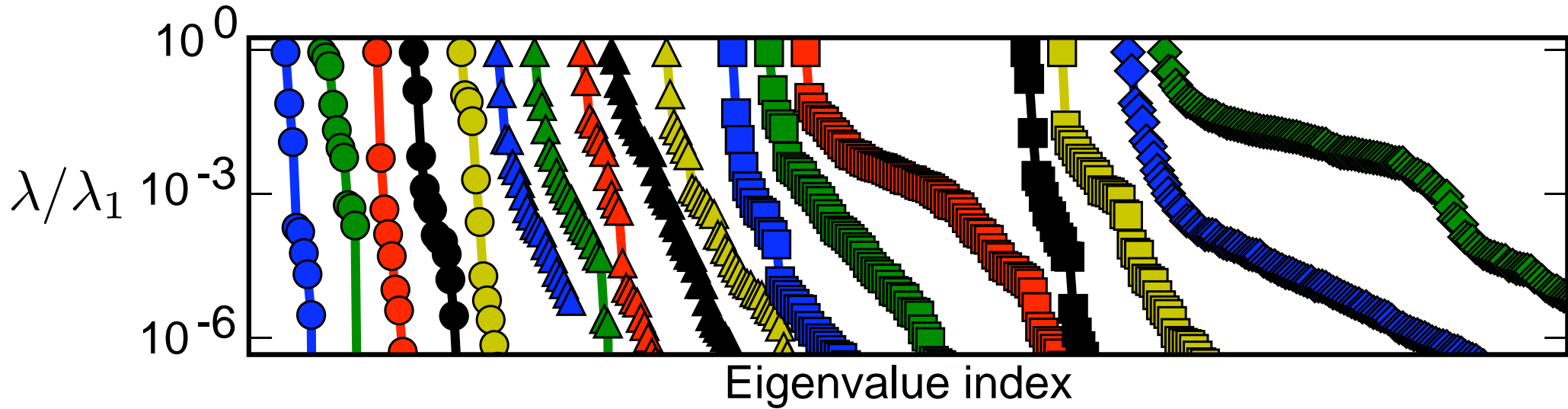


Quadratic approximation:

$$H_{i,j} \equiv \left. \frac{\partial^2 \chi^2(\theta)}{\partial \log \theta_i \partial \log \theta_j} \right|_{\theta^*}$$



Sloppiness in Biology



- | | | | |
|-----------------------|------------------------|--------------------------|-----------------------|
| ● Tyson 1991 (9) | ▲ Kholodenko 2000 (21) | ■ Ueda 2001 (49) | ◆ Chen 2004 (131) |
| ● Zwolak 2005 (11) | ▲ Lee 2003 (22) | ■ Locke 2005 (61) | ◆ Sasagawa 2005 (234) |
| ● Goldbeter 1991 (13) | ▲ Leloup 1999 (38) | ■ Zak 2003 (97) | |
| ● Vilar 2002 (15) | ▲ Brown 2004 (48) | ■ Curto 1998 (105) | |
| ● Edelstein 1996 (17) | ▲ von Dassow 2000 (49) | ■ Chassagnole 2002 (119) | |

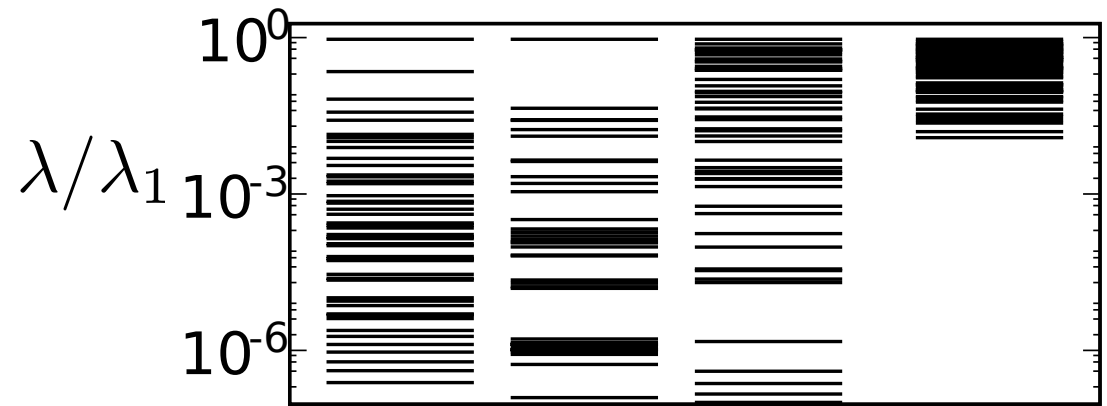
$$\chi^2(\theta) \propto \sum_{\substack{\text{species } s \\ \text{conditions } c}} \frac{1}{T_c} \int_0^{T_c} \left[\frac{y_{s,c}(\theta, t) - y_{s,c}(\theta^*, t)}{\sigma_s} \right]^2 dt$$

Sloppiness Elsewhere

Origins

Redundant basis for
parameters

Waterfall et al.
Phys. Rev. Lett. 97:15060 (2006),
arXiv:cond-mat/0605387



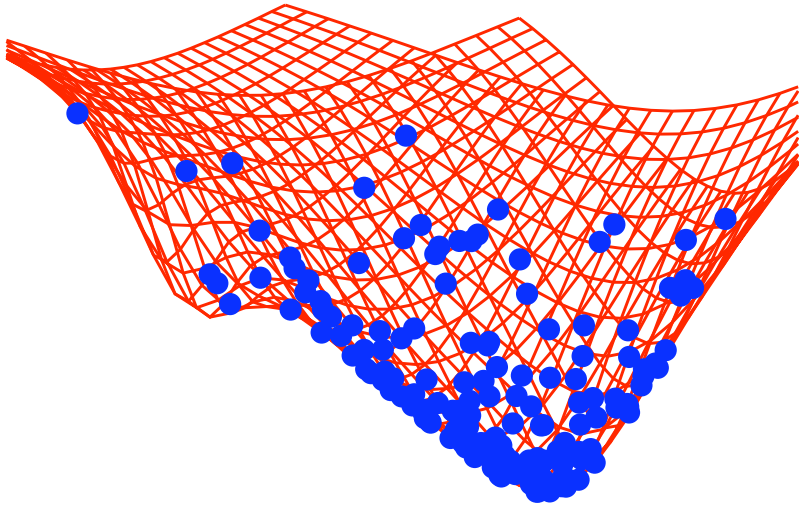
Quantum Monte Carlo† (47)
Energy Recovery Linact†† (213)
Sum of Exponentials (48)
Plane to Data (48)
(not sloppy)

† Cyrus Umrigar

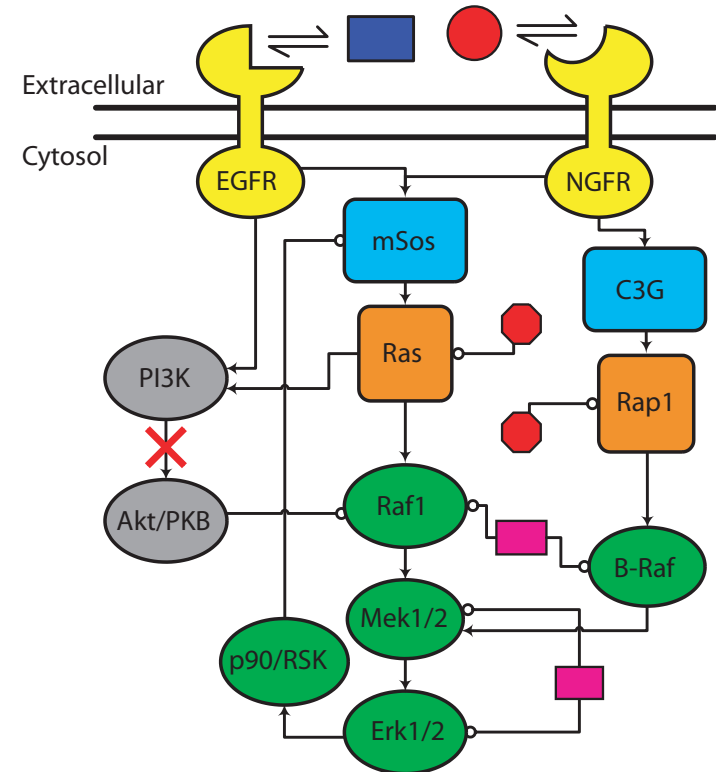
†† Georg Hoffstaetter, Chris Mayes

Falsifiable Predictions

Growth factor signaling in PC12 cells



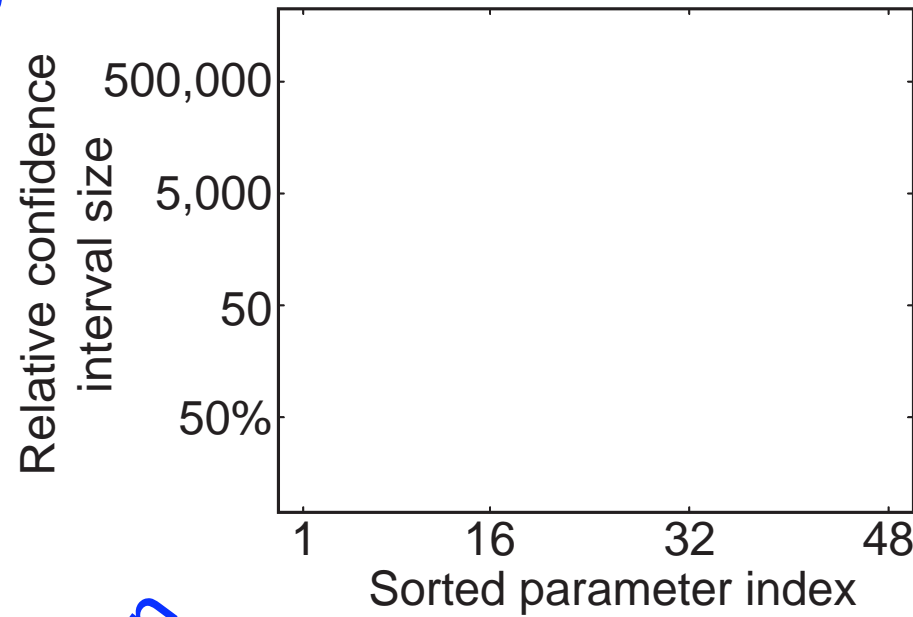
Calculate prediction uncertainties over an ensemble of parameter sets consistent with available data.



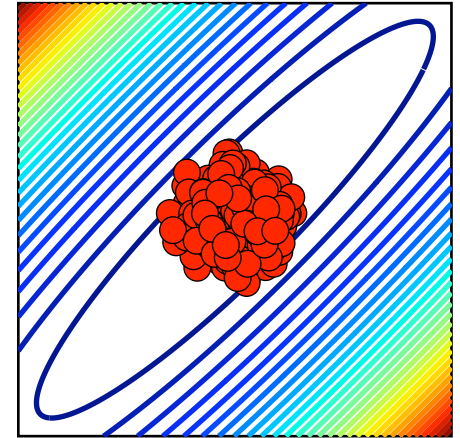
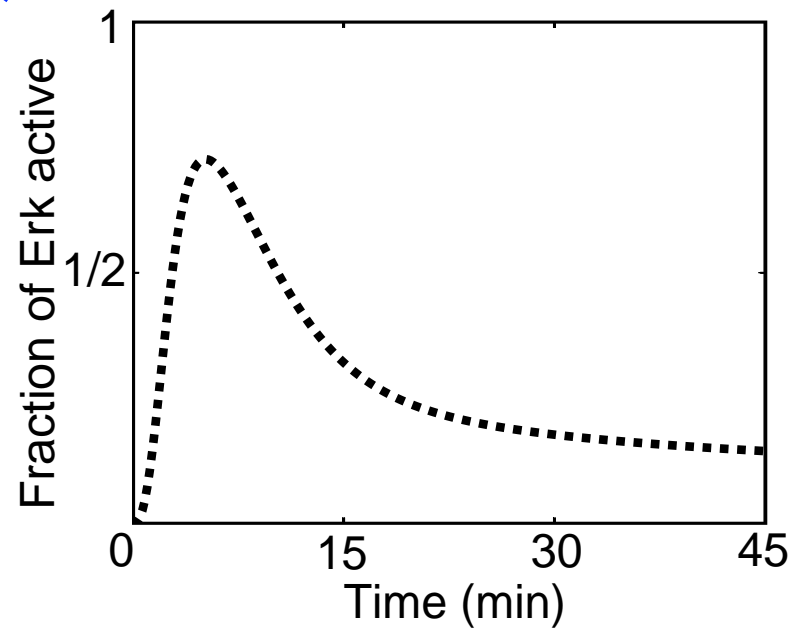
48 parameters

Uncertainties

Parameters

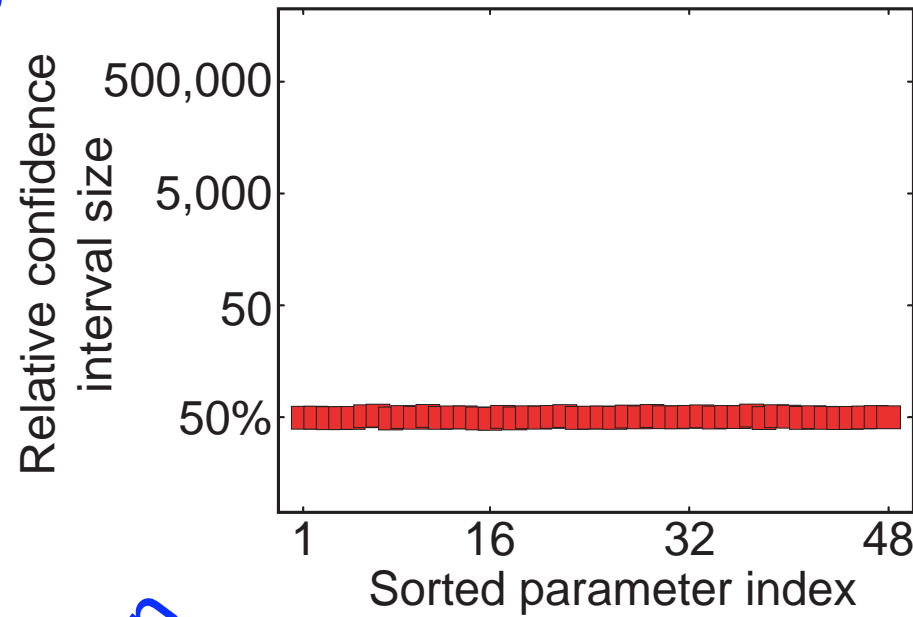


Prediction

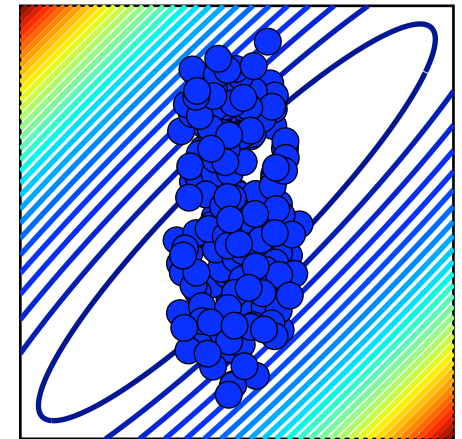
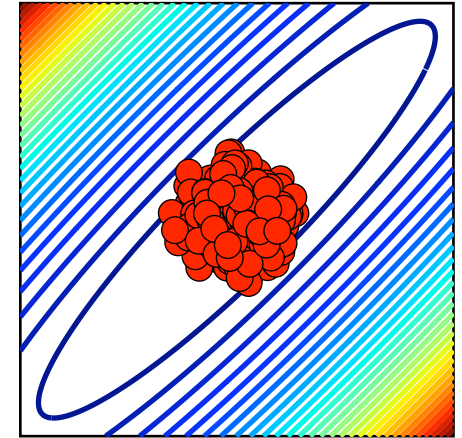
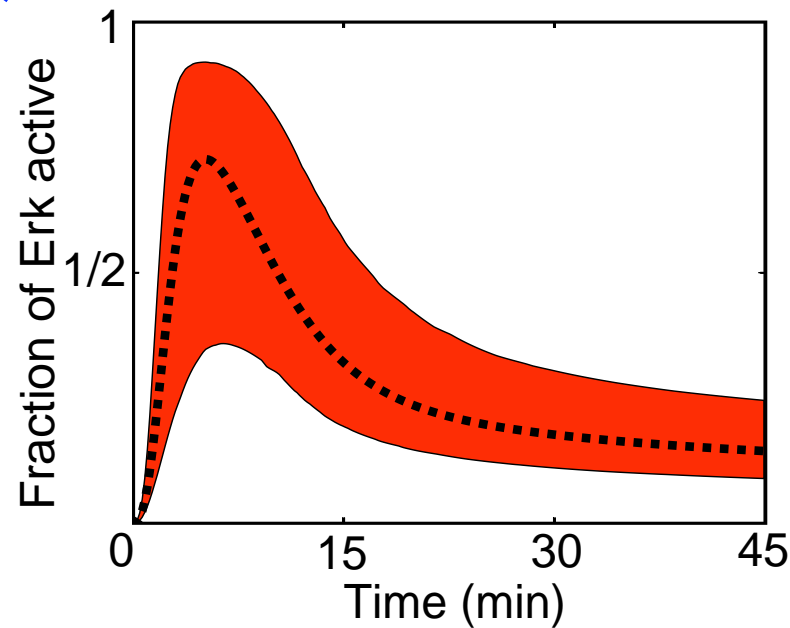


Uncertainties

Parameters

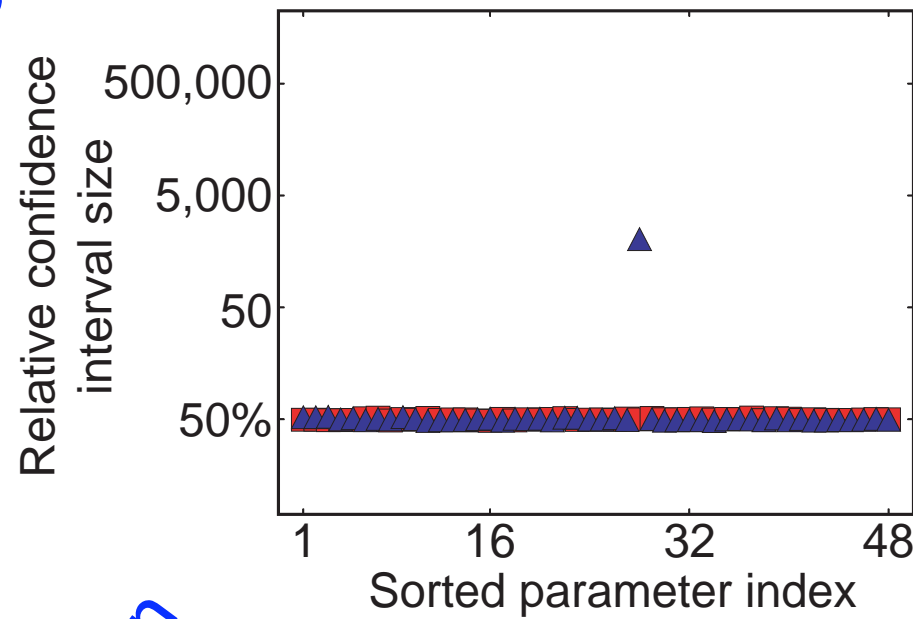


Prediction

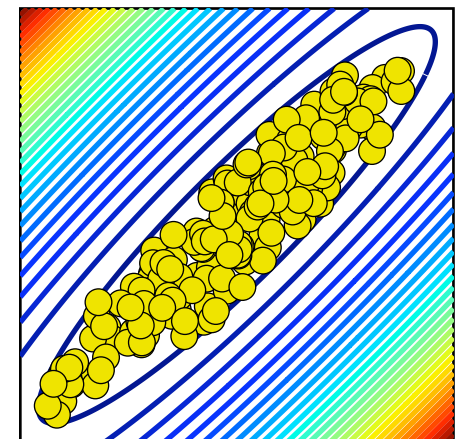
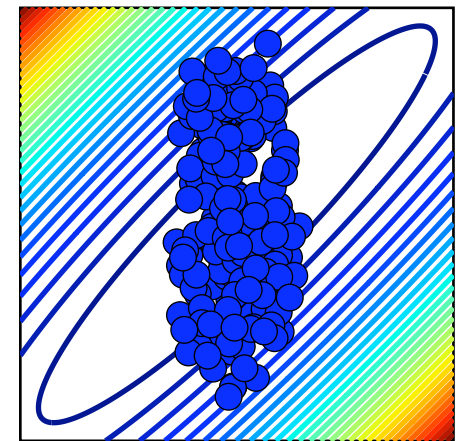
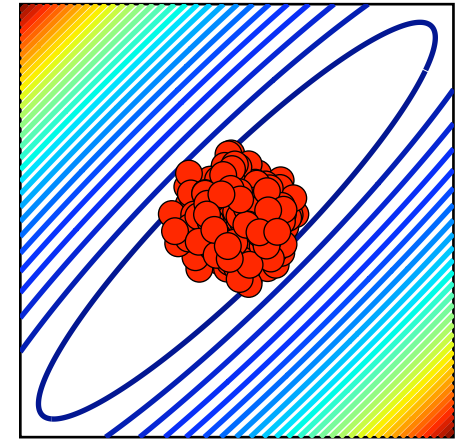
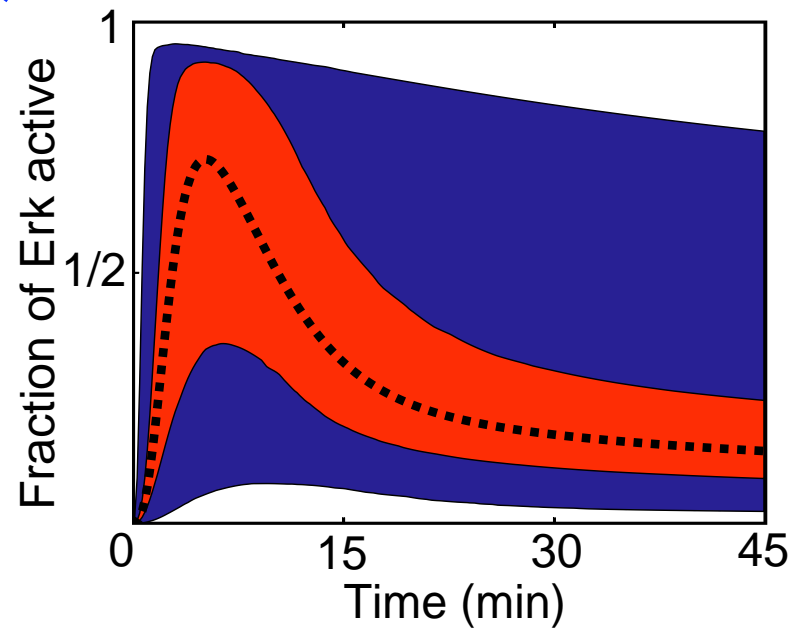


Uncertainties

Parameters

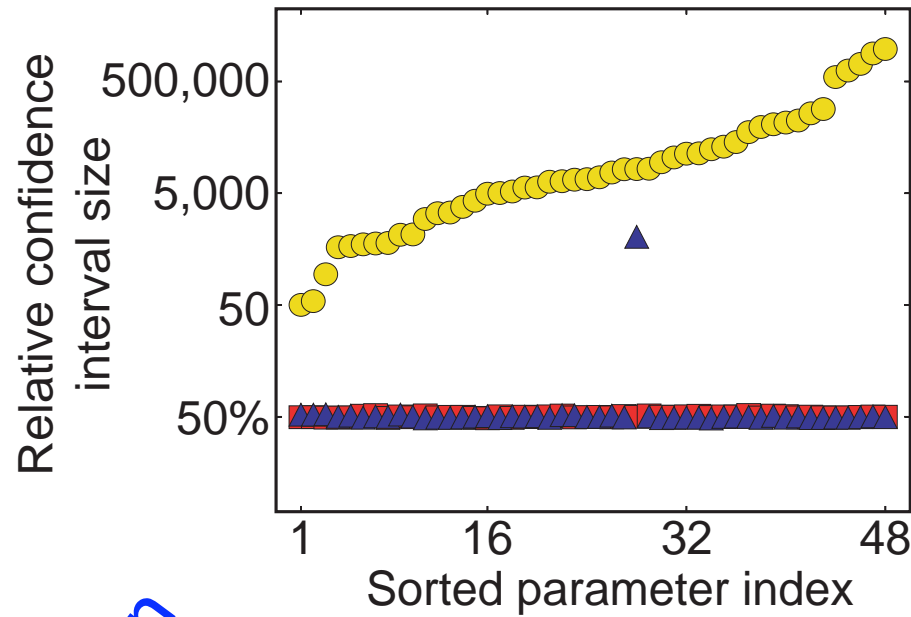


Prediction

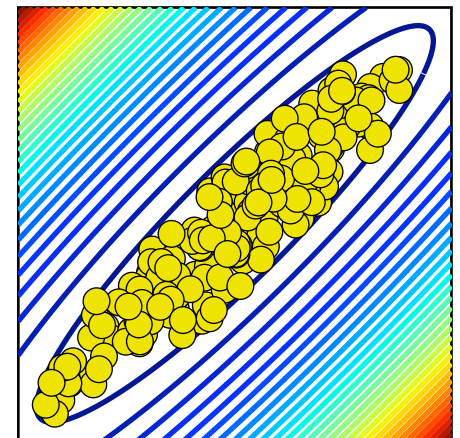
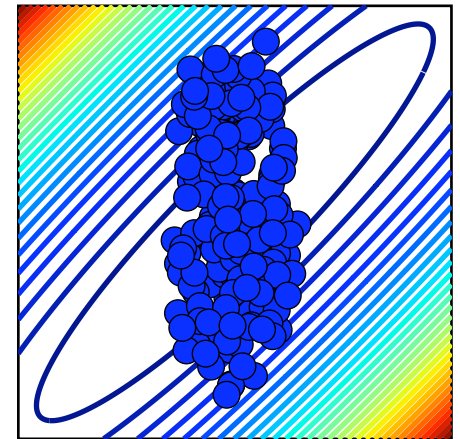
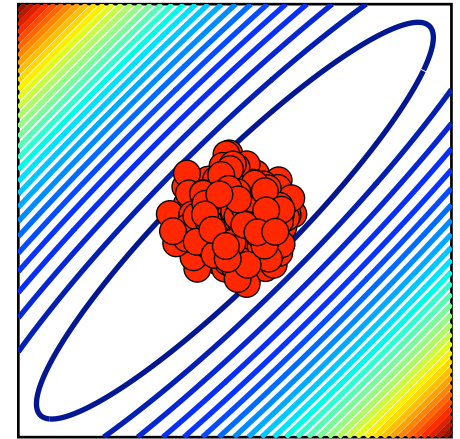
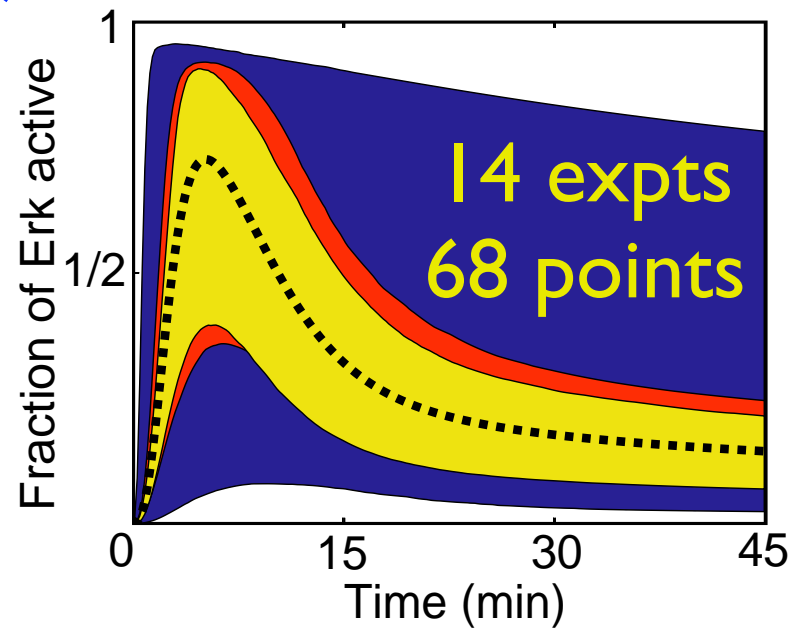


Uncertainties

Parameters

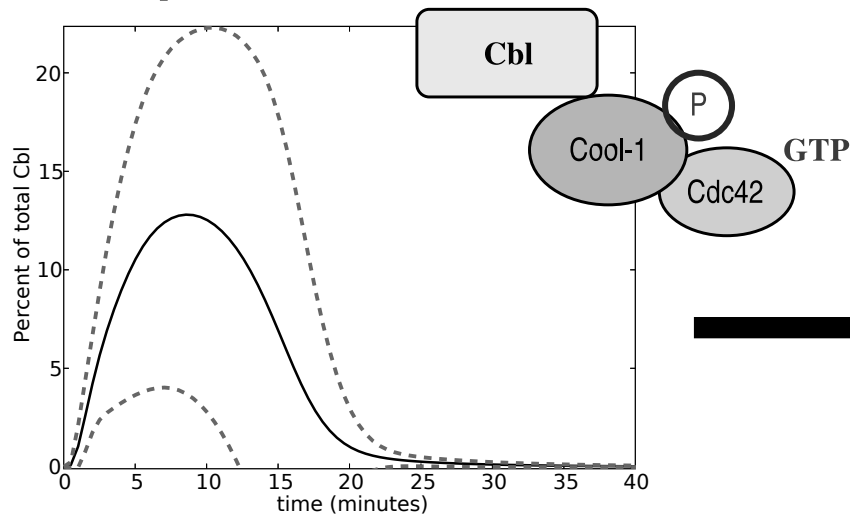


Prediction

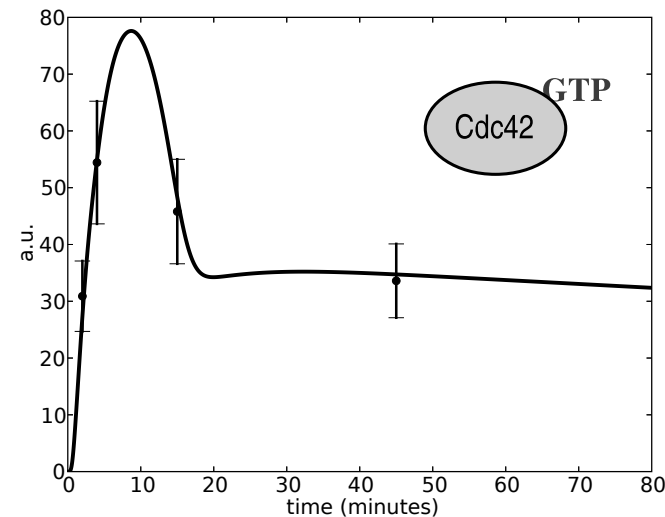


Refining Predictions

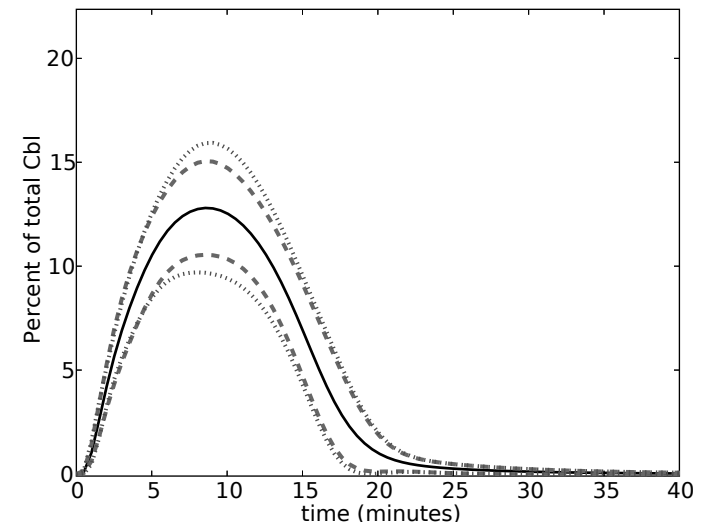
Loosely constrained
prediction



Optimized
experimental design



Usefully tight
prediction



Casey et al.
IEE Proc. Sys. Biol. in press,
arXiv:q-bio.MN/0610024

SloppyCell

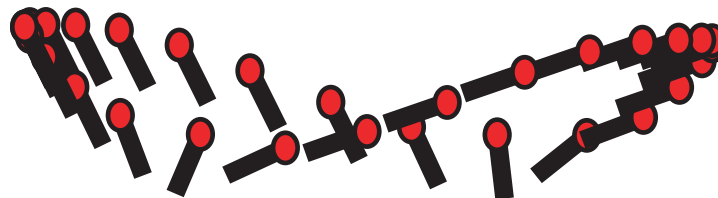
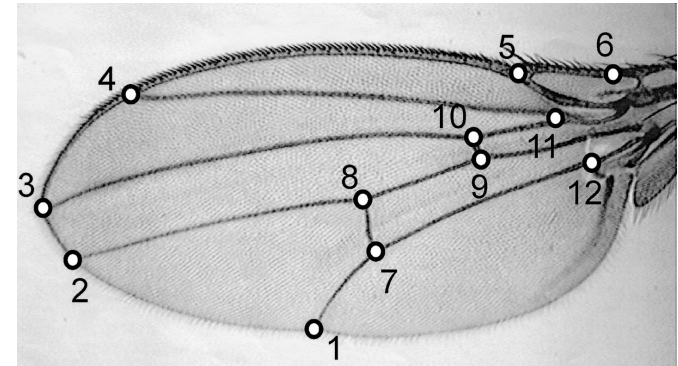
<http://sloppycell.sourceforge.net>

- Notable features
 - System Biology Markup Language import/export
 - Sensitivity integration ($dy(\theta, t)/d\theta_i$)
 - Parameter ensembles Markov-Chain Monte-Carlo with importance sampling
 - Parallel execution via MPI
 - F2Py interface to Fortran DAE integrator
- with Jordan Atlas, Bob Kuczenski and Kevin Brown

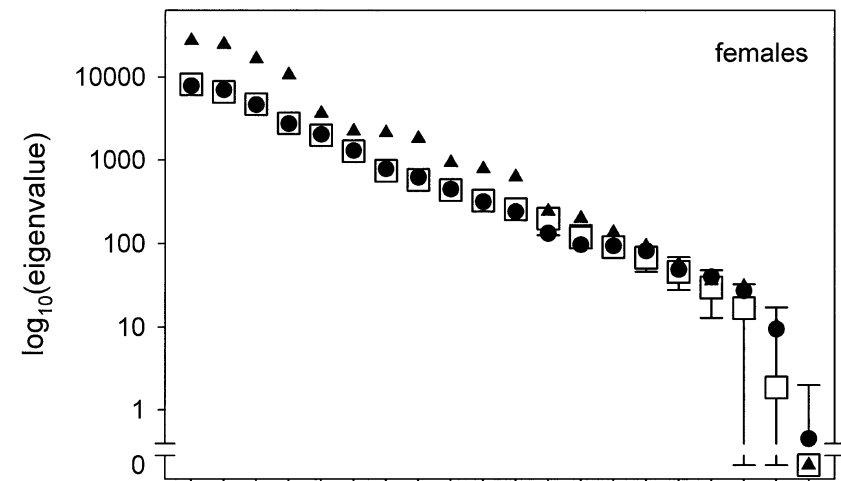
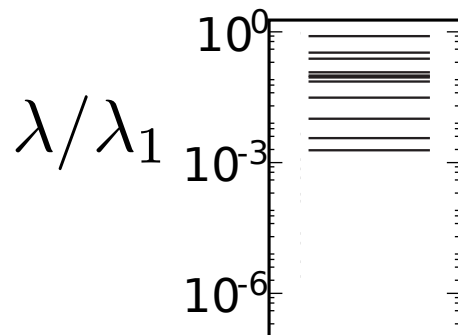


Hypothesis: Fitness is Sloppy

news.nationalgeographic.com



Berman and Wang
J. Fluid Mech. in press

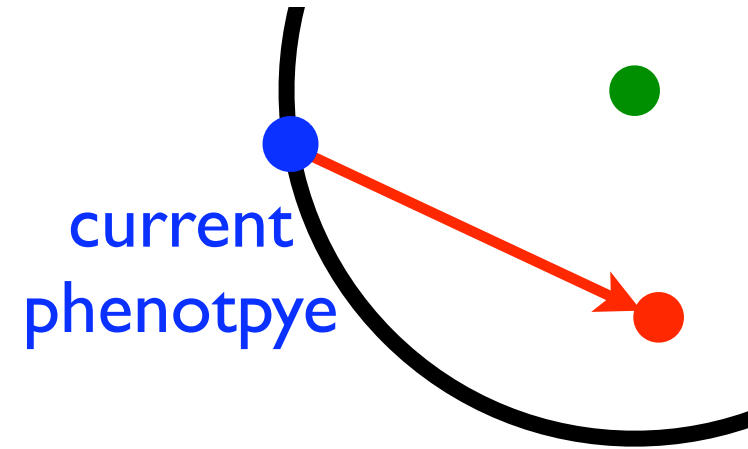
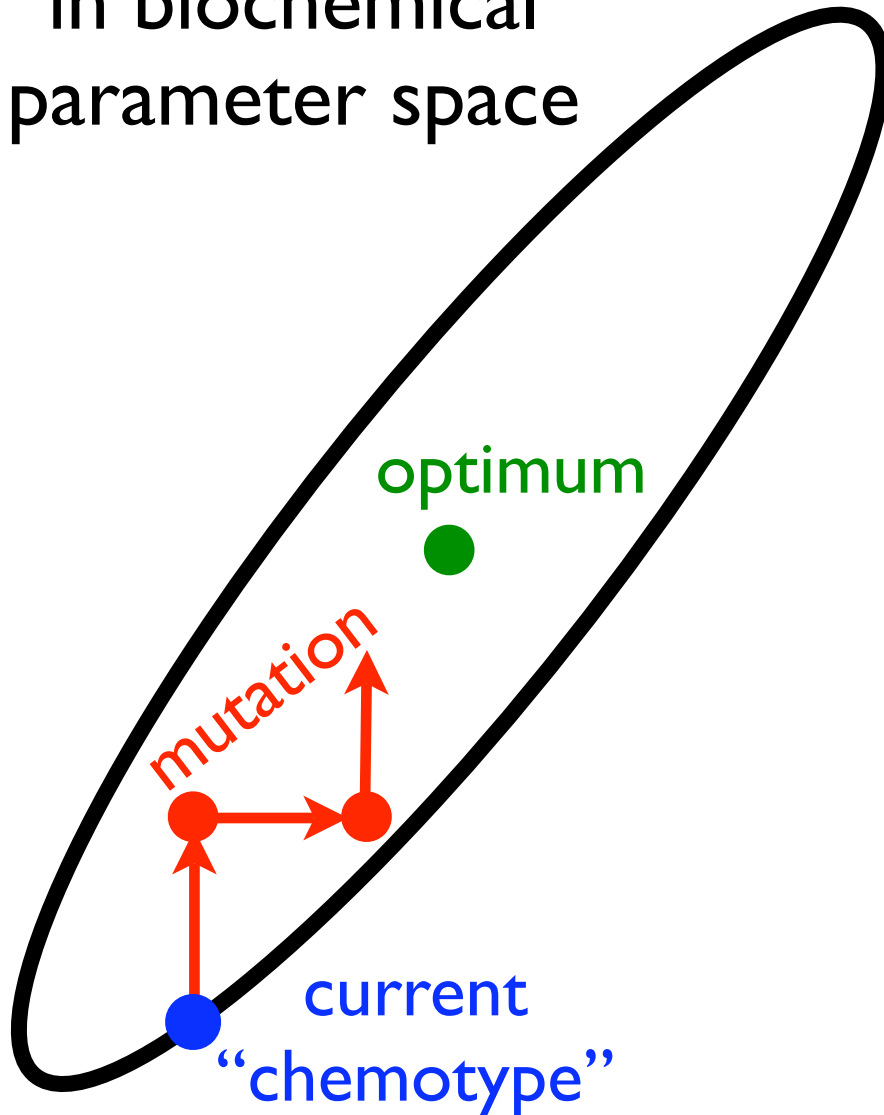


Mezey and Houle
Evolution 59:1027 (2005)

Logsdon et al.
in preparation

Our Evolution Model

Sloppy fitness contours
in biochemical
parameter space



Fisher's Geometrical Model (1930)

Circular fitness contours
in "trait" space

Connecting to Experiments

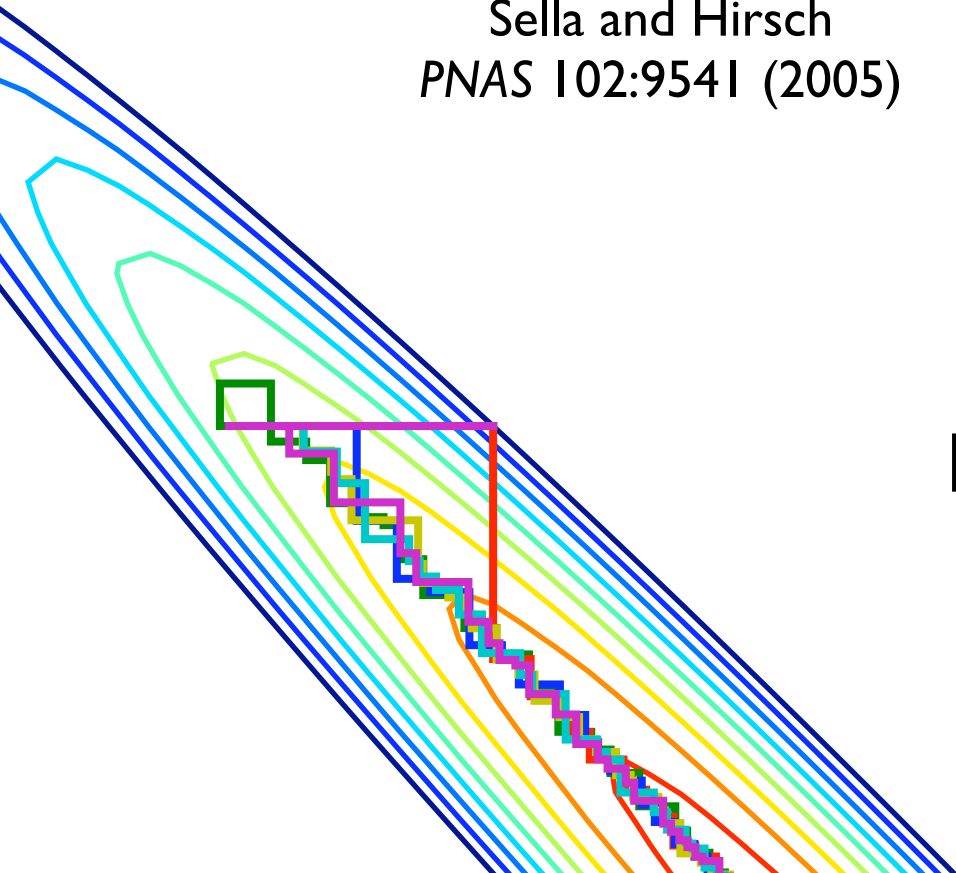
$$P_{i \rightarrow j} = \frac{1 - (W_i/W_j)^2}{1 - (W_i/W_j)^{2N}}$$

Sella and Hirsch
PNAS 102:9541 (2005)

Observe the first few adaptations of a microbial population to a new environment.

We seek analytic expressions for the distribution of fitness changes, in the Strong-Selection, Weak-Mutation limit.

Hypothesis: Population will often hop onto narrow ridge of high fitness. Finite population size may then become important.

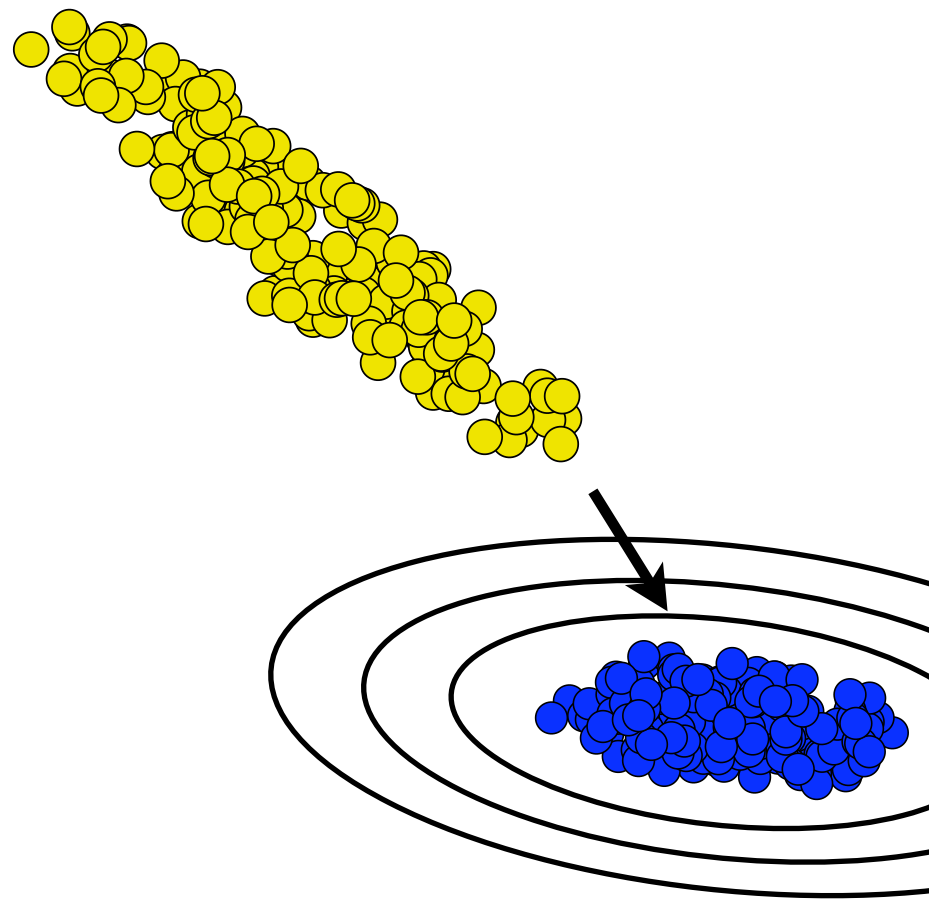


Linear Response

How does a population respond to gradual changes in the underlying fitness landscape?

Expand initial state into eigenvectors of the Markov process. Convergence dominated by the smallest eigenvalues.

$$\rho(\theta, t) = \rho^*(\theta) + e^{-\lambda_n t} c_n \rho_n(\theta)$$



Conclusions

Sloppiness is **universal** in complex biology.

Consequently, collective parameter fits most efficiently constrain model predictions.

We're exploring the implications for evolution in a simple model.

rng7@cornell.edu

Thanks

Sloppiness

Eric Siggia

John Guckenheimer

Modeling

Rick Cerione

Jon Erickson

Evolution

Carl Franck

